Congenital Diaphragmatic Hernia Overview

Animal Models of CDH

Animal models make it easier to understand the pathogenesis of congenital diaphragmatic defects and the associated pulmonary hypoplasia.

Surgical models. The first animal models widely used were surgical models of CDH. In these models, hernias were surgically induced in the diaphragms of developing fetuses (most commonly sheep, but the procedure has been extended to rodents) [Del Borrello et al 1983, Lipsett et al 1997]. Although this model cannot be used to study the cause of CDH, it has been useful for evaluating the effect of compression and decreased diaphragmatic activity on lung development.

Nitrofen. Administration of the herbicide nitrofen to pregnant rats reliably produces Bochdalek diaphragmatic hernia and bilateral pulmonary hypoplasia. Nitrofen (2,4-dichlorophenyl 4-nitrophenyl ether) is a polyhalogenated aromatic compound with structural similarity to thyroid hormone [Kluth et al 1990]. Although its mechanism of teratogenesis is unknown, evidence suggests that nitrofen is acting through the retinoic acid signaling pathway [Greer et al 2000, Babiuk et al 2003, Greer et al 2003]. The phenotype produced in rats closely resembles that found in humans in diaphragm type, pulmonary hypoplasia, and associated cardiovascular malformations, though it is not known whether the mechanisms of pathogenesis are comparable. Nitrofen is no longer commercially available as a herbicide for agricultural applications in the US.

Vitamin A. In several different species, dietary deficiency of vitamin A (retinol) can lead to a spectrum of malformations, often including congenital diaphragm defects. In the nitrofen model, administration of vitamin A ameliorates its teratogenic effect, reducing the frequency and severity of CDH in exposed rat fetuses [Thebaud et al 1999]. Retinoic acid receptor knock-out mice, null for both the alpha- and beta- receptor subtypes, demonstrate CDH [Mendelsohn et al 1994]. One small human study showed decreased levels of retinol in newborns with CDH compared to controls [Major et al 1998]. These various lines of evidence suggest that abnormalities in vitamin A metabolism could be associated with congenital diaphragm defects.

Genetic models. Mouse genetic models are useful in unraveling the pathogenesis of CDH. In an ENU mutagenesis screen, a mutation in Fog2 was discovered to cause posterolateral diaphragmatic eventration with primary pulmonary hypoplasia [Ackerman et al 2005]. Human mutations in FOG2 were previously reported to cause congenital heart defects such as tetralogy of Fallot and atrial ventricular valve defects [Tevosian et al 2000]. Recently, a mutation in

FOG2 was found in an infant who died at birth with a clinical diagnosis of CDH and respiratory failure and who, at autopsy, was found to have a deep posterior diaphragmatic eventration and severe bilateral pulmonary hypoplasia. This infant had a de novo heterozygote stop mutation in FOG2 [Ackerman et al 2005]. This is the first discovery of a genetic cause of nonsyndromic CDH in humans. This finding, together with the animal model, suggests that the pulmonary hypoplasia has a primary component in some cases.

Mutations in Wt1, Wilms tumor 1 gene, also cause diaphragmatic defects in mice [Kreidberg et al 1993]. Although mutations in human WT1 were not found in a small series of nonsyndromic CDH cases, a mutation in WT1 has been associated with CDH in a few cases of Denys-Drash syndrome [Devriendt et al 1995, Devriendt et al 1996] and one case of Meacham syndrome [Reardon et al 2004].

Other genetic mouse models include models in which the central tendon is disrupted [Liu et al 2003, Yuan et al 2003] and models with abnormal muscularization [Epstein et al 2000, Babiuk & Greer 2002]. Although these models have not been directly associated with defects in humans with CDH, they will help in understanding the normal embryogenesis of the diaphragm.